Support for the amendment to claim 40 can be found, for example, at page 14, lines 24 to 26 of the present specification. Claim 43 has been amended to correct the language of the Markush Group. In particular the claim has been amended to recite the word "and" instead of "or" between the last two members of the Markush Group. Claim 43 has further been amended to correct a typographical error in the recitation of nucleotide positions. An example of support for this amendment can be found in Table 20 of the present specification. New claim 44 has been added to more clearly point out what Applicants consider the invention. An example of support for new claim 44 can be found, *inter alia*, at page 88, line 1 to page 90, line 10.

Thus, claims 36-44 are presently pending in the instant Application.

THE REJECTIONS UNDER 35 U.S.C. § 112 SHOULD BE WITHDRAWN

Claims 40-43[1] were rejected under section 112, first paragraph, of Title 35 of the United States Code allegedly for lack of enabling support in the specification. The Examiner bases this rejection on the allegation that the specification does not provide evidence that every embodiment of the claimed invention has the claimed properties. Applicants contend that this rejection is in error and that the full scope of the claimed invention is enabled by the instant specification.

Claims 40 and 41 recite an attenuated RSV particle with at least one M2-1 gene mutation that results in the exchange of a cysteine amino acid for an amino acid selected from the following group: glycine, valine, aspartic acid or alanine. Claims 42 and 43 recite an attenuated RSV particle with a C-terminal truncated M2-1 protein. The specification provides ample guidance to one skilled in the art to mutate the M2-1 gene of RSV to result in an RSV particle with the claimed mutations (see, *e.g.*, the specification at Section 5.4, pages 20 to 23, and Section 12, pages 87 to 91). The specification provides ample guidance to one skilled in the art to rescue or recover the mutated RSV particles (see, *e.g.*, the specification at Section 5.3, pages 19 to 20, and Section 6, pages 27 to 30). The specification also provides ample guidance to one skilled in the art to determine whether or not the recovered mutated RSV particle has an attenuated phenotype (see, *e.g.*, the specification at Section 5.4, pages 20

[1] Although Office Action mailed October 22, 2002 recites "claims 41 and 41", Applicants believe that the rejection was made in connection with claims 40 and 41 because both claims relate to exchanging cysteine residues in the M2-1 protein.

to 23). The specification specifically provides that "an attenuated RSV exhibits a substantially lower degree of virulence as compared to a wild-type virus, including a slower growth rate, such that the symptoms of viral infection do not occur in an immunized individual" (see, the specification at page 20, lines 29 to 31). The specification further provides that the attenuated RSV particles may be used as vaccines (see, the specification at page 24, line 25 to page 27, line 18).

One skilled in the art armed with the instant specification would be able to mutate the M2-1 gene as claimed. The instant specification describes particularly how to make the claimed mutants, even providing the primers needed to mutate each cysteine codon in the M2-1 gene (see, the specification at page 88, Table 18). Once the mutants are generated and the mutated RSV particle recovered, one skilled in the art would be able to determine if the mutant RSV particle has an attenuated phenotype, *i.e.*, a slower growth rate than a wild-type RSV particle.

The specification exemplifies the claimed invention in the Working Examples. Example 12 (pages 88 to 91 of the specification) demonstrates that an RSV particle with a M2-1 gene product with a mutated cysteine residue (Cys 96) or an RSV particle with a truncated M2-1 gene product has an attenuated phenotype. Thus, confirming that the claimed invention is fully enabled by the instant specification.

The Examiner points to post filing art to demonstrate the alleged non-enablement of the claimed invention (Hardy *et al.*, 2000, J. of Virology 74:5880-5885; Collins *et al.*, 1999, Virology 259:257-255). However, neither Hardy nor Collins provide any evidence concerning the claimed invention. Hardy describes two mutants where a cysteine residue of M2-1 is substituted with a serine residue. Collins does not describe any mutation of the M2-1 gene. Thus, Applicants fail to see the relevance of these references to the claimed invention.

A patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless there is reason to doubt the objective truth of the teachings which must be relied on for enabling support. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971); In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). Here the Examiner can point to no such reason.

Claim 43 is rejected under section 112, first paragraph, because one of the recited codons consists of 4 nucleotides. Applicants respectfully point out that this rejection is moot in view of the present amendment; the nucleotide position "7993" has been corrected to read

"7992" as supported by Table 20. The stop codon as recited in amended claim 43 consists of 3 nucleotides.

Claims 40 and 41 are rejected under section 112, first paragraph, because, according to the Examiner, the specification as filed allegedly lacks written description support. In response, Applicants respectfully invite the Examiner's attention to page 24, lines 12-18, where support for the recitation of valine, aspartic acid and alanine as substitutes for cysteine can be found.

Applicants assert that the instant specification in combination with information readily available to the skilled artisan at the time the instant application was filed fully enables the claimed invention and that the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. 103 SHOULD BE WITHDRAWN

Claims 40 and 41 are rejected under 35 U.S.C. § 103(a) as obvious over Worthington *et al.*, 1996 (Proc. Natl. Acad. Sci. U.S.A. 93:13754-13759; "Worthington") in view of Howorka and Bayley, 1998 (BioTechniques 25:764-766; "Howorka"). The gravamen of the rejection is that Worthington teaches that the cysteine residue of the M2-1 gene are part of a structurally conserved motif and that it would have been obvious to mutagenize this motif using the method taught in Howorka to test the function of the motif. In response, Applicants contend that the cited references do not make obvious the claimed RSV mutants and that the rejection under 35 U.S.C. § 103 should be withdrawn.

A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention, and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. In re O'Farrell 853 F.2d 894, 903 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicants' disclosure. In re Vaeck 947 F.2d 488 (Fed. Cir. 1991).

In the present instance, the relavant inquiry is first, whether the cited art suggested an attenuated RSV with a M2-1 gene mutated to encode a gene product wherein a cysteine

residue is replaced with a glycine, valine, aspartic acid or alanine. Even assuming *arguendo* that the prior art provided a suggestion to mutate the conserved motif described in Worthington, neither Worthington nor Howorka suggest substituting the cysteine residue with a glycine, valine, aspartic acid or alanine. Worthington simply describes that the RSV M2-1 gene has a motif which is conserved among zinc binding proteins. Howorka describes the wide-spread use of site directed mutagenesis to determine the structural and functional relationships of proteins.

The second inquiry is whether the prior art references provide one of ordinary skill in the art with a reasonable expectation of success. In re O'Farrell; In re Vaeck, supra. Applicants assert that the cited references fail to provide such an expectation. Neither reference, taken alone or in combination, provides any indication that mutating the M2-1 gene would have any effect on the life cycle of RSV. Certainly neither Worthington nor Howorka alone or in combination suggest that a virus with the claimed mutations would have an attenuated phenotype.

In view of the foregoing, the cited prior art references, alone or in combination, do not make obvious the claimed invention. Therefore, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

Applicant respectfully requests that the amendments and remarks of the present response be entered and made of record in the instant application. Withdrawal of the Examiner's rejections and an allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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Enclosures